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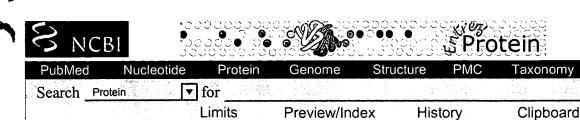
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1: AAC97073. MEK kinase 1 [Hom...[gi:2815888] BLink, Domains, Links 1495 aa linear PRI 17-DEC-1998 AAC97073 LOCUS MEK kinase 1 [Homo sapiens]. DEFINITION AAC97073 ACCESSION AAC97073.1 GI:2815888 VERSION locus AF042838 accession AF042838.1 DBSOURCE KEYWORDS Homo sapiens (human) SOURCE ORGANISM Homo sapiens Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo. REFERENCE (residues 1 to 1495) Xia, Y., Wu, Z., Su, B., Murray, B. and Karin, M. **AUTHORS** JNKK1 organizes a MAP kinase module through specific and sequential TITLE interactions with upstream and downstream components mediated by its amino-terminal extension Genes Dev. 12 (21), 3369-3381 (1998) **JOURNAL** MEDLINE 99026111 9808624 **PUBMED** (residues 1 to 1495) REFERENCE **AUTHORS** Xia, Y., Su, B. and Karin, M. TITLE Direct Submission Submitted (13-JAN-1998) Pharmacology, University of California at **JOURNAL** San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA Method: conceptual translation supplied by author. COMMENT Location/Qualifiers **FEATURES** 1..1495 source /organism="Homo sapiens" /db xref="taxon:9606" /cell_type="T cells; B cells" Protein <1..1495 /product="MEK kinase 1" /name="protein kinase MEKK1" CDS 1..1495 /gene="MEKK1" /coded_by="AF042838.1:<1..4488" ORIGIN 1 pspeaggggg alkassaraa aagllreags ggreradwrr rqlrkvrsve ldqlpeqplf 61 laasppasst spspepadaa gsgtgfqpva vppphgaasr rgahltesva apdsgasspa 121 aaepgekrap aaepspaaap agremenket lkglhkmddr peermirekl katcmpawkh 181 ewlerrnrrg pvvvkpipvk gdgsemnhla aespgevqas aaspaskgrr spspgnspsg 241 rtvksespgv rrkrvspvpf qsgritpprr apspdgfspy speetnrrvn kvmrarlyll 301 qqigpnsfli ggdspdnkyr vfigpqncsc ahgtfcihll fvmlrvfqle psdpmlwrkt 361 lknfeveslf qkyhsrrssr ikapsrntiq kfvsrmsnsh tlsssststs ssensikdee 421 eqmcpicllg mldeesltvc edgcrnklhh hcmsiwaeec rrnreplicp lcrskwrshd 481 fyshelsspv dspsslraaq qqtvqqqpla gsrrnqesnf nlthygtqqi ppaykdlaep 541 wiqvfgmelv gclfsrnwnv remalrrlsh dvsgalllan gestgnsggs sgsspsggat 601 sgssqtsisg dvveaccsvl smvcadpvyk vyvaalktlr amlvytpchs laeriklqrl 661 lqpvvdtilv kcadansrts qlsistllel ckgqagelav greilkagsi giggvdyvln 721 cilgnqtesn nwqellgrlc lidrlllefp aefyphivst dvsqaepvei rykkllsllt

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Revised: August 5, 2002.

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L1	6288142	1	L1

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 20020172940 A1

L6: Entry 1 of 3

File: PGPB

Nov 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020172940

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020172940 A1

TITLE: Methods and reagents for isolating biologically active peptides

PUBLICATION-DATE: November 21, 2002

INVENTOR-INFORMATION:

NAME CITY

STATE COUNTRY

RULE-47

Gyuris, Jeno

Winchester

MA US

Morris, Aaron J. Boston MA US

US-CL-CURRENT: 435/5; 435/7.1, 435/7.32, 436/518, 530/324, 530/350

Full Title Citation Front Review Classification Date Reference Sequences Attachments Claims KWC Draw Desc Image

☐ 2. Document ID: US 20020025536 A1

L6: Entry 2 of 3

File: PGPB

Feb 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020025536

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020025536 A1

TITLE: Methods and reagents for isolating biologically active antibodies

PUBLICATION-DATE: February 28, 2002

INVENTOR-INFORMATION:

NAME CITY STATE COUNTRY RULE-47

Gyuris, Jeno Winchester MA US
Ewert, Sebastian-Meier Wolfratshausen MA DE
Nagy, Zolton Wolfratshausen DE
Morris, Aaron Brighton US

US-CL-CURRENT: 435/7.1; 435/5, 435/69.1

Full Title Citation Front Review Classification Date Reference Sequences Attachments Claims KVMC Draw Desc Image

3. Document ID: US 6420110 B1

L6: Entry 3 of 3

File: USPT

Jul 16, 2002

US-PAT-NO: 6420110

DOCUMENT-IDENTIFIER: US 6420110 B1

TITLE: Methods and reagents for isolating biologically active peptides

Full Title Citation	Front Review	Classification Da	te Reference	Sequences	Attachments	Claims	KWIC	Drawi Desc	Image
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 NEWS 11 Jun 10 PCTFULL has been reloaded
 NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment
 NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;
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 NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY
 NEWS 15 Jul 30 NETFIRST to be removed from STN
 NEWS 16 Aug 08 CANCERLIT reload
 NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18 Aug 08 NTIS has been reloaded and enhanced
 NEWS 19 Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE)
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 NEWS 22 Aug 26 Sequence searching in REGISTRY enhanced
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 NEWS 23 Sep 03
 NEWS 24 Sep 16 Experimental properties added to the REGISTRY file
 NEWS 25 Sep 16 CA Section Thesaurus available in CAPLUS and CA
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 NEWS 28 Oct 24 BEILSTEIN adds new search fields
 NEWS 29 Oct 24 Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 30 Oct 25 MEDLINE SDI run of October 8, 2002
 NEWS 31 Nov 18 DKILIT has been renamed APOLLIT
 NEWS 32 Nov 25 More calculated properties added to REGISTRY
 NEWS 33 Dec 02 TIBKAT will be removed from STN
 NEWS 34 Dec 04 CSA files on STN
 NEWS 35 Dec 17 PCTFULL now covers WP/PCT Applications from 1978 to date
 NEWS 36 Dec 17 TOXCENTER enhanced with additional content
 NEWS 37 Dec 17 Adis Clinical Trials Insight now available on STN
 NEWS 38 Dec 30 ISMEC no longer available
 NEWS 39 Jan 13 Indexing added to some pre-1967 records in CA/CAPLUS
 NEWS 40 Jan 21 NUTRACEUT offering one free connect hour in February 2003
                 PHARMAML offering one free connect hour in February 2003
 NEWS 41 Jan 21
 NEWS 42 Jan 29
                 Simultaneous left and right truncation added to COMPENDEX,
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 NEWS 43 Feb 13 CANCERLIT is no longer being updated
              January 6 CURRENT WINDOWS VERSION IS V6.01a,
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L1 2054 MEKK1

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ANSWER 1 OF 1 HCAPLUS CO IGHT 2003 ACS
L3
AN
     2000:84978 HCAPLUS
DN
     132:133888
ТT
     Forkhead-associated domain protein MIF1 interacting with MEKK1 kinases and
     the gene encoding it and the regulation of the MEKK signal transduction
     Marcireau, Christophe; Multon, Marie-christine; Polard-housset, Valerie
IN
PA
     Rhone-Poulenc Rorer S.A., Fr.
SO
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RE.CNT 2
             THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
             ALL CITATIONS AVAILABLE IN THE RE FORMAT
=> D AB
    ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
L3
    The present invention relates to a novel protein of the MEKK signal
AΒ
     transduction pathway, and the gene encoding it. The invention further
     relates to diagnostic and therapeutic uses of the protein or the gene, and
     to methods of screening for agonists or antagonists of the protein,
    particularly with respect to MEKK activity. In particular, the invention
    provides a gene encoding MIF1, the MIF1 protein, and antibodies that
    specifically bind MIF1. MIF1 and the MIF1 gene can be used in screening
    assays, particularly to identify agonists and antagonists of MIF1
    interaction with MEKK, and thus modulators of the MEKK signal pathway.
    MIF1 gene (or cDNA) can also be delivered to cells, e.g., for in vitro
    screening or testing, or in vivo or ex vivo for gene therapy. The protein
    was identified using a two-hybrid screen. The mRNA was found in all
    tissues tested and was most abundant in heart, pancreas and placenta with
    evidence of alternate splicing in the placenta.
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           83 L1 (10A) HUMAN
=> S L4 (10A) (DNA OR GENE? OR NUCLE?)
  2 FILES SEARCHED...
  5 FILES SEARCHED...
  7 FILES SEARCHED...
 10 FILES SEARCHED...
           17 L4 (10A) (DNA OR GENE? OR NUCLE?)
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=> DUP REM L5

PROCESSING COMPLETED FOR L5

12 DUP REM L5 (5 DUPLICATES REMOVED)

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     ANSWER 1 OF 12 HCAPLUS
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     2002:978087 HCAPLUS
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     Gene expression profiles for diagnosis of breast cancer patients and
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     Dai, Hongyue; He, Yudong; Linsley, Peter S.; Mao, Mao; Roberts,
IN
     Christopher J.; Van't Veer, Laura Johanna; Van de Vijver, Marc J.;
     Bernards, Rene; Hart, A. A. M.
     Rosetta Inpharmatics, Inc., USA
PA
SO
     PCT Int. Appl., 187 pp.
     CODEN: PIXXD2
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L6
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AN
     2002:505721 HCAPLUS
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     137:245071
     Activation of human monoamine oxidase B gene expression by a protein
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     kinase C MAPK signal transduction pathway involves c-Jun and Egr-1
     Wong, Wai K.; Ou, Xiao-Ming; Chen, Kevin; Shih, Jean C.
ΑU
    Department of Molecular Pharmacology and Toxicology, School of Pharmacy,
CS
     University of Southern California, Los Angeles, CA, 90089-9121, USA
     Journal of Biological Chemistry (2002), 277(25), 22222-22230
SO
     CODEN: JBCHA3; ISSN: 0021-9258
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LA
RE.CNT 41
             THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L6
     ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2003 ACS
                                                      DUPLICATE 1
AN
     2001:10070 HCAPLUS
DN
     134:82715
     Antisense modulation of MEKK1 expression for therapeutic application
ΤI
     Monia, Brett P.; Gaarde, William; Ward, Donna T.; Cowsert, Lex M.
IN
     Isis Pharmaceuticals, Inc., USA
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CF, CG, CI, CM, GA N, GW, ML, MR, NE, SN, TD, TG 20020502 EP 2000-947557 20000720 EP 1200573 A1 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL PRAI US 1999-359756 Α 19990723 WO 2000-US19747 W 20000720 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD RE.CNT 19 ALL CITATIONS AVAILABLE IN THE RE FORMAT ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2003 ACS L6 AN2001:728869 HCAPLUS DN 136:18304 Expression of human cystatin A by keratinocytes is positively regulated ΤI via the Ras/MEKK1/MKK7/JNK signal transduction pathway but negatively regulated via the Ras/Raf-1/MEK1/ERK pathway ΑU Takahashi, Hidetoshi; Honma, Masaru; Ishida-Yamamoto, Akemi; Namikawa, Kazuhiko; Kiyama, Hiroshi; Iizuka, Hajime Department of Dermatology, Asahikawa Medical College, Asahikawa, 078-8510, CS Japan SO Journal of Biological Chemistry (2001), 276(39), 36632-36638 CODEN: JBCHA3; ISSN: 0021-9258 PB American Society for Biochemistry and Molecular Biology DTJournal English LA RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT DUPLICATE 2 L6 ANSWER 5 OF 12 MEDLINE MEDLINE AN2001290699 PubMed ID: 11244091 DN MEK7-dependent activation of p38 MAP kinase in keratinocytes. ΤI Dashti S R; Efimova T; Eckert R L ΑU CS Departments of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106-4970, USA. JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Mar 16) 276 (11) 8059-63. SO Journal code: 2985121R. ISSN: 0021-9258. CY United States Journal: Article: (JOURNAL ARTICLE) DT LA English FS Priority Journals 200106 EΜ Entered STN: 20010625 ED Last Updated on STN: 20030105 Entered Medline: 20010621 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2003 ACS L₆ 2001:506424 HCAPLUS AN DN 135:240015 Distinctive gene expression profiles associated with Hepatitis B virus ΤI .times. protein Wu, Chuan-Ging; Salvay, David M.; Forgues, Marshonna; Valerie, Kristoffer; ΑU Farnsworth, Julie; Markin, Rodney S.; Wang, Xin Wei Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, CS MD, 20892-4255, USA so Oncogene (2001), 20(28), 3674-3682 CODEN: ONCNES; ISSN: 0950-9232 PB Nature Publishing Group DTJournal English TιA RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2003 ACS L6 2001:867565 HCAPLUS AN 136:116484 DN Modulation of human cytomegalovirus immediate-early gene enhancer by ΤI mitogen-activated protein kinase kinase kinase-1 Sun, Bin; Harrowe, Greg; Reinhard, Christoph; Yoshihara, Corinne; Chu, ΑU Keting; Zhuo, Shaoqiu

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Chiron Corporation, CA, 94 2916, USA
CŞ
SO
     Journal of Cellular Biochemistry (2001), 83(4), 563-573
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RE.CNT 27
              THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
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     ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2003 ACS
L6
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     Forkhead-associated domain protein MIF1 interacting with MEKK1 kinases and
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     Marcireau, Christophe; Multon, Marie-christine; Polard-housset, Valerie
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             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9955057
                      A1
                            20000214
                                          AU 1999-55057
                                                            19990721
     EP 1100913
                      Α1
                            20010523
                                          EP 1999-941444
                                                            19990721
            AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
                                           JP 2000-561308
                                                            19990721
     JP 2002524026
                      T2
                            20020806
PRAI US 1998-93590P
                      Р
                            19980721
     WO 1999-EP5142
                      W
                            19990721
              THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE.CNT 2
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
     ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2003 ACS
L6
AN
     2000:192958 HCAPLUS
DN
     132:306670
     The gene MAPK8IP1, encoding islet-brain-1, is a candidate for type 2
TΤ
     Waeber, Gerard; Delplanque, Jerome; Bonny, Christophe; Mooser, Vincent;
AU
     Steinmann, Myriam; Widmann, Christian; Maillard, Anne; Miklossy, Judith;
     Dina, Christian; Hani, El Habib; Vionnet, Nathalie; Nicod, Pascal; Boutin,
     Philippe; Froguel, Philippe
     Department of Internal Medicine, CHUV-University Hospital, Lausanne,
CS
     Switz.
     Nature Genetics (2000), 24(3), 291-295
SO
     CODEN: NGENEC; ISSN: 1061-4036
PΒ
     Nature America
DT
     Journal
     English
T.A
              THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE.CNT 29
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
L6
     ANSWER 10 OF 12 WPIDS (C) 2003 THOMSON DERWENT
     1999-508649 [42]
AN
                       WPIDS
     1999-571843 [48]; 2002-462905 [49]
CR
                       DNC C1999-148629
    N1999-379027
DNN
     A new mammalian serine-threonine protein kinase for treating disorder
ΤI
     characterized by aberration of the enzyme gene.
DC
     B04 D16 S03
IN
     JOHNSON, G L
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(CADU-N) CADUS PHARM CORP; AJE-N) NAT JEWISH CENT IMMUNOL
PĄ
     RESPIRATORY
CYC
    84
_{\mathtt{PI}}
     WO 9941385
                   A1 19990819 (199942)* EN 105p
                                                     C12N015-54
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
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         W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD
            GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV
            MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
            UA UG US UZ VN YU ZW
     AU 9932895
                   A 19990830 (200003)
                                                     C12N015-54
     US 2002146798 A1 20021010 (200269)
                                                     C12N009-12
    WO 9941385 A1 WO 1999-US2974 19990212; AU 9932895 A AU 1999-32895
ADT
     19990212; US 2002146798 Al Provisional US 1998-78153P 19980316,
     Provisional US 1998-99165P 19980904, Cont of US 2000-423890 20000306, US
     2001-864 20011031
FDT
    AU 9932895 A Based on WO 9941385
                      19980213
PRAI US 1998-23130
     ICM C12N009-12; C12N015-54
          A61K031-00; A61K048-00; C07H021-04; C07K016-40; C07K019-00;
          C12N005-06; C12N005-10; C12N015-62; C12P021-02; C12Q001-68;
          G01N033-573
     ANSWER 11 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
L6
AN
     2000:103400 BIOSIS
DN
     PREV200000103400
     MEKK1 suppresses oxidative stress-induced apoptosis of embryonic stem
ΤI
     cell-derived cardiac myocytes.
     Minamino, Tetsuo; Yujiri, Toshiaki; Papst, Philip J.; Chan, Edward D.;
ΑU
     Johnson, Gary L.; Terada, Naohiro (1)
     (1) Department of Pathology, University of Florida College of Medicine,
CS
     Gainesville, FL, 32610 USA
     Proceedings of the National Academy of Sciences of the United States of
SO
     America, (Dec. 21, 1999) Vol. 96, No. 26, pp. 15127-15132.
     ISSN: 0027-8424.
DТ
     Article
LA
    English
    English
SL
     ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2003 ACS
L6
     1998:638916 HCAPLUS
AN
DN
     129:340468
     Regulation of human involucrin promoter activity by a protein kinase C,
TI
     Ras, MEKK1, MEK3, p38/RK, AP1 signal transduction pathway
ΔII
     Efimova, Tatiana; LaCelle, Peter; Welter, Jean F.; Eckert, Richard L.
     Department of Physiology and Biophysics, Case Western Reserve University
CS
     School of Medicine, Cleveland, OH, 44106-4970, USA
     Journal of Biological Chemistry (1998), 273(38), 24387-24395
SO
     CODEN: JBCHA3; ISSN: 0021-9258
     American Society for Biochemistry and Molecular Biology
PB
DT
     Journal
     English
LΑ
RE.CNT 82
              THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
=> D 10-12 AB
     ANSWER 10 OF 12 WPIDS (C) 2003 THOMSON DERWENT
L6
          9941385 A UPAB: 20021031
AΒ
     NOVELTY - A MEK kinase, designated MEKK1, is new.
          DETAILED DESCRIPTION - Isolated polypeptides (P1 and P2 respectively)
     comprise:
          (a) a fragment of a polypeptide comprising the 1493 (I) or 1302 (II)
     amino acid (aa) sequence (given in the specification);
          (b) a naturally occurring allelic variant of a polypeptide comprising
     sequence (I) or (II), encoded by a nucleic acid molecule (NAM) which
     hybridizes under stringent conditions to respectively the 5253 (III) or
     3911 (IV) nt sequence (given in the specification);
```

- (c) a polypeptide encoded by sequence III or IV, and (d) a polypeptide comprising sequence (I) or (II).

INDEPENDENT CLAIMS are also included for the following:

- (1) isolated NAM's (N1 and N2 respectively) comprising:
- (a) a fragment of at least 100 contiguous nt of sequence (III) or (IV);
 - (b) the nt sequence of (III) or (IV), or their complement;
 - (c) a NAM encoding a polypeptide comprising (I) or (II);
- (d) a NAM encoding a polypeptide comprising at least 15 contiguous aa residues of (I) or (II);
- (e) a NAM encoding a natural allelic variant of (I) or (II), which hybridizes under stringent conditions to (III) or (IV), respectively;
- (f) a nucleic acid antisense to the coding strand of a NAM having sequence (III) or (IV), respectively;
 - (2) a host cell containing N1 or N2;
- (3) a fusion protein of P1 or P2 operatively linked to heterologous aa sequences;
 - (4) an antibody which selectively binds to P1 or P2;
 - (5) producing P1 or P2 by culturing the host cell;
 - (6) detecting a MEKK1 polypeptide in a sample by:
- (a) contacting the sample with a compound which selectively binds the polypeptide, and
 - (b) detecting bound compound;
 - (7) detecting presence of a MEKK1 nucleic acid in a sample by:
- (a) contacting the sample with a nucleic acid probe or primer which selectively binds the nucleic acid, and
 - (b) detecting bound probe or primer;
- (8) detecting biological activity of a MEKK1 polypeptide in a sample by contacting the sample with an agent capable of detecting MEKK1
- (9) modulating MEKK1 activity by contacting a cell with an agent that modulates MEKK1 activity, particularly an antibody that binds MEKK1 protein or a nucleic acid antisense to MKEKK1 mRNA;
- (10) detecting a genetic alteration characterized by aberrant modification or mutation of a gene encoding a MEKK1 protein, and/or mis-regulation of that gene, and/or aberrant post-translational modification of a MEKK1 protein, where a wild-type form of that gene encodes a protein with MEKK1 activity;
- (11) an isolated active fragment of a MEKK1 protein which mediates apoptosis, comprising an amino acid sequence at least 75% homologous to about residues 875-1493 of sequence (I);
- (12) an isolated protease-resistant MEKK1 protein, comprising a sequence at least 75% homologous to sequence (I), where at least one aa equivalent to residues 871-874 is substituted such that the MEKK 1 protein is resistant to proteolysis by a caspase after amino acid 874;
- (13) an isolated NAM encoding an active fragment of a MEKK1 polypeptide that mediates apoptosis, and comprising a sequence at least 75 (preferably 95)% homologous to about nt 2637-4493 of sequence (III);
- (14) an isolated NAM encoding the protease-resistant MEKK1 protein of (12);
 - (15) an expression vector comprising the NAM of (13) or (14);
 - (16) a host cell comprising one of the expression vectors;
- (17) an isolated NAM encoding a protease-resistant MEKK1 protein comprising (II), with at least one codon encoding an aa equivalent to at least one of aa 681-684 of (II), so that the encoded protein is resistant to proteolysis by a caspase after an aa equivalent to 681-684;
- (18) stimulating apoptosis in a cell comprising introducing an expression vector encoding a MEKK1 active fragment;
- (19) inhibiting apoptosis in a cell comprising introducing protease-resistant MEKK1 protein;
- (20) generating a MEKK1 active fragment in vitro, comprising contacting a MEKK1 protein with a caspase protease under proteolysis conditions, and allowing the MEKK1 protein to be cleaved to generate an active fragment, and
- (21) identifying a compound that modulates proteolytic cleavage of a MEKK1 protein by caspase protease comprising contacting the protein and protease with a candidate compound and determining the effect of the compound on proteolytic cleavage.

ACTIVITY - Regulatory: MEKK1 functions to integrate proteases and

signal transduction pathwa to regulate cellular apoptosis MECHANISM OF ACTION - nzymatic: MEKK proteins are serme-threonine protein kinases that phosphorylate and regulate MEK proteins.

USE - A MEKK1 modulator is used to treat a disorder characterized by aberrant MEKK1 protein or nucleic acid expression or activity (claimed).

ADVANTAGE - None given

Dwg.0/25

L6

L6

AΒ

ANSWER 11 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. A combination of in vitro embryonic stem (ES) cell differentiation and targeted gene disruption has defined complex regulatory events underlying oxidative stress-induced cardiac apoptosis, a model of postischemic reperfusion injury of myocardium. ES cell-derived cardiac myocytes (ESCM) having targeted disruption of the MEKK1 gene were extremely sensitive, relative to wild-type ESCM, to hydrogen peroxide-induced apoptosis. In response to oxidative stress, MEKK1-/- ESCM failed to activate c-Jun kinase (JNK) but did activate p38 kinase similar to that observed in wild-type ESCM. The increased apoptosis was mediated through enhanced tumor necrosis factor alpha production, a response that was positively and negatively regulated by p38 and the MEKK1-JNK pathway, respectively. Thus, MEKK1 functions in the survival of cardiac myocytes by inhibiting the production of a proapoptotic cytokine. MEKK1 regulation of the JNK pathway is a critical response for the protection against oxidative stress-induced apoptosis in cardiac myocytes.

ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2003 ACS Involucrin is a marker of keratinocyte terminal differentiation. Our previous studies show that involucrin mRNA levels are increased by the keratinocyte differentiating agent, 12-0-tetradecanoylphorbol-13-acetate (TPA) (Welter, J. F., Crish, J. F., Agarwal, C., and Eckert, R. L. (1995) J. Biol. Chem. 270, 12614-12622). We now study the signaling cascade responsible for this regulation. Protein kinase C and tyrosine kinase inhibitors inhibit both the TPA-dependent mRNA increase and the TPA-dependent increase in hINV promoter activity. The relevant response element is located within the promoter proximal regulatory region and includes an AP1 site, AP1-1. Co-transfection of the hINV promoter with dominant neg. forms of Ras, MEKK1, MEK1, MEK7, MEK3, p38/RK, and c-Jun inhibit the TPA-dependent increase. Wild type MEKK1 enhances promoter activity and the activity can be inhibited by dominant neg. MEKK1, MEK1, MEK7, MEK3, p38/RK, and c-Jun. In contrast, wild type Raf-1, ERK1, ERK2, MEK4, or JNK1 produced no change in activity and the dominant neg. forms of these kinases failed to suppress TPA-dependent transcription. Treatment with an S6 kinase (S6K) inhibitor, or transfection with constitutively active S6K produced relatively minor changes in promoter activity, ruling out a regulatory role for S6K. These results suggest that activation of involucrin transcription involves a pathway that includes protein kinase C, Ras, MEKK1, MEK3, and p38/RK. Addnl. pathways that transfer MEKK1 activation via MEK1 and MEK7 also may function, but the downstream targets of these kinases need to be identified. AP1 transcription factors appear to be the ultimate target of this regulation.

=> DIS HIS

L4

(FILE 'HOME' ENTERED AT 23:08:33 ON 14 FEB 2003)

FILE 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS, ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 23:08:45 ON 14 FEB 2003
L1 2054 S MEKK1
L2 0 S L1 AND PY=1993
L3 1 S L1 (10A) PLACENTA

L5 17 S L4 (10A) (DNA OR GENE? OR NUCLE?) L6 12 DUP REM L5 (5 DUPLICATES REMOVED)

=> LOG H
COST IN U.S. DOLLARS
FULL ESTIMATED COST

83 S L1 (10A) HUMAN

SINCE FILE TOTAL ENTRY SESSION 43.90 44.11 DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY TOTAL SESSION

CA SUBSCRIBER PRICE

-1.30

-1.30

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 23:18:11 ON 14 FEB 2003